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Is acne a sign of androgen excess disorder or not?

Gulsum Uysal[a,*], Yılmaz Sahin[b], Kursad Unluhizarci[c], Ayten Ferahbas[d], Semih Zeki Uludag[b], Ercan Aygen[b], Fahrettin Kelestimur[c]

[a] Department of Obstetrics and Gynecology, Adana Numune Education and Research Hospital, Adana, Turkey
[b] Department of Obstetrics and Gynecology, Erciyes University Medical School, Kayseri, Turkey
[c] Department of Endocrinology, Erciyes University Medical School, Kayseri, Turkey
[d] Department of Dermatology, Erciyes University Medical School, Kayseri, Turkey

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ABSTRACT

Objective: Acne is not solely a cosmetic problem. The clinical importance of acne in the estimation of androgen excess disorders is controversial. Recently, the Amsterdam ESHRE/ASRM-sponsored third PCOS Consensus Workshop Group suggested that acne is not commonly associated with hyperandrogenemia and therefore should not be regarded as evidence of hyperandrogenemia. Our aim was to investigate whether acne is a sign of androgen excess disorder or not.

Study design: This is a cross sectional study that was performed in a university hospital involving 207 women, aged between 18 and 45 years, suffering mainly from acne. The women were assigned as polycystic ovary syndrome (PCOS), idiopathic hirsutism (IH), idiopathic hyperandrogenemia (IHA). Women with acne associated with any of the androgen excess disorders mentioned above were named as hyperandrogenemia associated acne (HAA). Women with acne but without hirsutism and hyperandrogenemia and having ovulatory cycles were named as "isolated acne". Serum luteinizing hormone, follicle stimulating hormone, estradiol, progesterone, 17-hydroxyprogesterone, dehydroepiandrosterone-sulfate (DHEAS), androstenedione, total testosterone and lipid levels were measured.

Results: Acne score was similar between the women with isolated acne and HAA. The most common cause for acne was PCOS and only 28% of the women had isolated acne. 114 (55%) women had at least one raised serum androgen level.

Conclusions: In this study, 72% of acneic women had clinical and/or biochemical hyperandrogenemia. In contrast to the suggestion of ESHRE/ASRM-sponsored third PCOS Consensus Workshop Group, our data indicate that the presence of androgen excess disorders should be evaluated in women presenting with acne.

Introduction

Androgen excess is one of the most common endocrine disorders of premenopausal women and affects approximately 7% of the population [1]. It results in the development of androgenic features such as hirsutism, acne, androgenic alopecia and ovulatory dysfunction. Acne, which is a common disease of the skin, is characterized by increased sebum production, abnormal follicular epithelial differentiation, cornification obstructing the pilosebaceous follicle by desquamated epithelial cells and inflamation [2]. Various surveys have noted a relatively high prevalence of acne in the general population. The prevalence of acne is about 15% in all age groups and it is seen more frequently in women than men [3,4]. The relation of acne to increased serum androgens is not yet fully elucidated and the clinical importance of acne in the estimation of androgen excess disorders is controversial [5,6]. Although the prevalence of acne was investigated in various androgen excess disorders, there is not enough data regarding the relationship between acne and androgen excess disorders in patients presenting with acne alone. Thus, in this study our aim was to investigate what extend androgen excess disorder is responsible for acne in patients presenting with acne alone.

Abbreviations: PCOS, polycystic ovary syndrome; ESHRE/ASRM, European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine; IH, idiopathic hirsutism; IHA, idiopathic hyperandrogenemia; HAA, hyperandrogenemia associated acne; HOMA-IR, homeostasis model assessment-insulin resistance; DHEAS, dehydroepiandrosterone-sulfate; NCAH, non-classical congenital adrenal hyperplasia.

* Corresponding author at: Department of Obstetrics and Gynecology, Adana Numune Education and Research Hospital, Adana, 01170, Turkey.
E-mail address: gulsumaykut@yahoo.com (G. Uysal).

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Material and methods

This prospective study was conducted at Erciyes University Medical School. The patients were recruited between January 2011 and January 2012. Approval from the local Ethics Committee was obtained before the study and informed consent was obtained from the patients.

Study population

Two hundred seven women who were seen consecutively in outpatient clinic of Dermatology, aged between 18 and 45 years were included in the study. Since our aim was to investigate the relationship between acne and hyperandrogenemia, we have mainly recruited the patients suffering from acne alone. Acne was graded according to Lehmann's classification [7]. All the patients were evaluated for the presence/absence of other hyperandrogenic features and the presence of hirsutism was evaluated according to the modified Ferriman-Gallwey scoring system [8]. None of the patients was receiving any treatment for acne including hormonal and/or topical therapy, for at least three months before study. Also, the patients were not using glucocorticoids, antiandrogens, antidiabetics or any hormonal agent.

Patients with thyroid disease and hyperprolactinemia were not included in the study. We have measured serum luteinizing hormone, follicle stimulating hormone, estradiol, progesterone, 17-hydroxyprogesterone, DHEAS, androstenedione, total testosterone, in serum samples obtained in the morning during early follicular phase. Ovulation was confirmed by serum progesterone level in days 21–24 of menstrual cycle. Non-classical congenital adrenal hyperplasia (NCAH) was screened by using follicular phase serum 17-hydroxyprogesterone level and adrenocorticotropic hormone stimulation test was performed in 27 patients who had basal serum 17-hydroxyprogesterone level higher than 2 ng/dl [9,10]. Cushing's syndrome was excluded by dexamethasone suppression test in clinically suspected patients. Hyperandrogenemia was defined as testosterone, androstenedione and/or DHEAS levels were higher than 65 ng/dl, 2.9 ng/ml and 4410 ng/ml, respectively, according to the upper limit of the assays.

Since androgen excess disorders are associated with various forms of glucose intolerance, we have also performed oral glucose tolerance test to the patients. A 300-g carbohyrate diet was given for three days before the oral glucose tolerance test. After a basal blood sample was obtained, a 75-g glucose load was administered orally, and blood samples were obtained at 30-min intervals for two hours for the measurement of glucose. The presence of insulin resistance was investigated by homeostasis model assessment (HOMA) score. The estimate of insulin resistance by HOMA score was calculated with the formula: fasting serum insulin (IU/ml) x fasting plasma glucose (mmol/l)/22.5 [11].

The patients were assigned as polycystic ovary syndrome (PCOS), idiopathic hirsutism (IH), idiopathic hyperandrogenemia (IHA) and isolated acne. The diagnosis of PCOS was made according to ESHRE/ASRM criteria [12] and the diagnosis of IHA was made as previously described [13]. Briefly, IHA was diagnosed in hirsute patients with hyperandrogenemia, ovulatory cycles and normal ovaries after the exclusion of all other causes including adrenal/ovarian tumors and NCAH. Acne was evaluated by an experienced dermatologist (A.F) in outpatient clinic and pelvic ultrasonography for ovarian morphology was performed by an experienced gynecologist (Y.S). Patients with hirsutism, ovulatory menstrual cycles and normal serum androgen levels were considered as IH [14]. Patients with acne but without hirsutism and hyperandrogenemia and having ovulatory cycles were named as "isolated acne". Patients with acne associated with any of the androgen excess disorders described above were named as "hyperandrogenemia associated acne (HAA)" throughout the manuscript.

Assays

Serum samples for hormone levels were drawn after an overnight fast in the follicular phase of menstrual cycle. Serum samples were stored at −20 until assayed. Serum luteinizing hormone, follicle stimulating hormone and estradiol levels were determined by a two-site sandwich immunoassay using direct chemiluminometric method (Advia Centaur Sysytem), testosterone (DIAsource ImmunoAssays S.A, Nivelles, Belgium), DHEAS (DIAsource ImmunoAssays S.A, Nivelles, Belgium) and androstenedione (Immunotech, Prague, Czech Republic) levels were measured by radioimmunoassay.

Statistical analysis

The results were expressed as median and interquartile range (spanning the 25th to 75th percentiles), since the variables were not normally distributed. The groups were compared by using Mann-Whitney *U* test and Kruskal-Wallis analysis. Non-parametric Dunn test was also used for the comparison of multiple groups. The correlations were performed by Pearson's correlation analysis. Significance was considered when p was < 0.05.

Results

207 patients with acne were involved in the study. In all patients the primary reason for admission to the hospital was acne. Patients with HAA had significantly higher hirsutism score, total testosterone, DHEAS, androstenedione and HOMA-IR and lower follicle stimulating hormone levels than patients with isolated acne. Acne score was similar between the patients with isolated acne and HAA (Table 1). Insulin resistance, evaluated by HOMA-IR, was significantly ($p < 0.05$) higher (1.9 versus 1.5) in patients with HAA than patients with isolated acne (Table 1).

BMI: Body mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, HOMA-IR: The homeostatic model assessment insulin resistance, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, NS: Nonsignificant

82 (39.6%) of the patients had PCOS. None of the patients have been diagnosed as NCAH. As expected, patients with PCOS and IHA had higher serum androgen levels than other groups. 114 (55%) patients had at least one raised serum androgen level and there was no significant correlation between the severity of acne and hormonal values in all groups.

Although it did not reach a significant level, HOMA-IR was highest in PCOS women. The detailed data of the patients with various diagnoses are shown in Table 2. Patients with acne associated with/without hyperandrogenemia have similar serum lipid levels. Glucose intolerance was detected in 35 (23.4%) and 10 (17.2%) of the patients with HAA and isolated acne, respectively ($p > 0.05$).

PCOS: Polycystic ovary syndrome, IH: Idiopathic hirsutism, IHA: Idiopathic hyperandrogenemia, BMI: Body mass index, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, DHEAS: dehydroepiandrosterone sulfate, HOMA-IR: The homeostatic model assessment insulin resistance, LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, NS: Nonsignificant

Values are expressed as median (25%–75%) a,b,c: indicate statistical significance between different letters.

Table 1
Demographic and hormonal values of the patients suffering from isolated acne and acne associated with androgen excess disorders.

	Hyperandrogenemia associated acne n = 149(72%)	Isolated acne n = 58 (28%)	P value
Age (years)	21 (19–24)	22 (20–24)	NS
Hirsutism score	8 (6–13)	4 (4–5)	<0.01
Acnes core	1 (1–2)	1 (1–2)	NS
BMI(kg/m2)	21.8 (20–23.3)	21.6 (19–24.1)	NS
FSH(mIU/ml)	5.4 (4.4–6.7)	6.0 (5.1–7.3)	<0.05
LH(mIU/ml)	5.6 (3.9–7.5)	5 (4–6.6)	NS
Estradiol(pg/ml)	46 (36–57)	46(34–56)	NS
T.Testosterone (ng/dl)	82 (64–102)	53 (45–60)	<0.01
DHEAS (ng/ml)	2796 (2033–3392)	2173 (1656–2551)	<0.01
Androstenedione (ng/ml)	2.3 (1.7–2.8)	1.5 (1.2–1.8)	<0.01
HOMA-IR	1.9 (1.3–3)	1.5 (1–2.5)	<0.05
Total cholesterol(ng/dL	161 (144–181)	155 (146–176)	NS
LDL-C(ng/dl)	103 (92–120)	101 (96–114)	NS
HDL-C(ng/dl)	49 (43–57)	50 (47–57)	NS
Triglyceride(ng/dl)	90 (80–100)	89 (76–99)	NS

Discussion

Acne is the most common disease of the skin and may not only cause cosmetic problem but may also be a sign of an underlying disease. Despite the amount of research, the pathogenesis of acne is not completely understood. Follicular epidermal hyperproliferation, sebum excess, presence and amplified activity of propionibacterium acne and inflammation contribute to acne lesions [15].

Androgens play an important role in the development of cutaneous features. The development of early acne in the prepubertal period has been associated with elevated serum levels of DHEAS, a precursor for testosterone [16,17]. Furthermore, androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne [18]. However, the predictive role of acne for hyperandrogenic disorders is still debated. Azziz et al. [1] evaluated over 1000 consecutive patients consulting for symptoms potentially related to androgen excess. Acne was the sole complaint or finding in 4.8% of hyperandrogenic patients evaluated. That prevalance is remarkably lower than other studies, possibly due to including only hyperandrogenic patients. In the present study which was designed to ascertain the prevalance of various androgen excess disorders, and included 207 consecutive women suffering from acne, only 28% was detected as isolated acne. In other words, 72% of the patients had one of the androgen excess disorders and the most common cause of HAA was PCOS.

The data regarding the prevalence of PCOS in patients with acne are scarce and biased by the different criteria used to define the disease. Androgen Excess and PCOS Society Task Force reported that the prevalence of PCOS among women with acne only (excluding patients with hirsutism) is not high [19]. However, most studies of acne patients have simply reported selected features (e.g., polycystic ovaries on ultrasound, androgen levels, degrees of menstrual dysfunction, and so forth), and have not carefully addressed the prevalence of PCOS using current criteria.

Eden et al. [20] reported that of the 90 subjects presenting with acne, 67 (74%) were found to have PCOS. Timpatanapong and Rojanasakul [21] found PCOS in 19 out of 51 (37.3%) patients with acne and suggest that all women presenting with acne should be asked about their menstrual pattern and examined for other signs of hyperandrogenemia. Ozdemir et al. [22] investigated the biochemical and metabolic abnormalities in relation to cutaneous features of PCOS in 115 patients. They found that acne was not associated with the hormonal, metabolic and anthropometric variables and they suggest that acne is not a good marker for hyperandrogenism. In the light of their data, although the authors comment on that acne is not a good marker of hyperandrogenism, they have found acne in 53% of their PCOS patients which was the second most common symptom.

Table 2
Demographic and hormonal values of the patients suffering from acne according to underlying causes.

	PCOS n = 82 (39.6%)	IHA n = 49 (23.7%)	IH n = 18 (8.7%)	Isolated acne n = 58 (28%)	P value
Age (years)	21 (19–23)	21 (19–23)	23 (18–25)	22 (20–14)	NS
Hirsutism score	9 (6–12)ab	6 (4–12)b	11 (8–13)a	4 (4–5)c	< 0.05
Acnes core	2 (1–2)	1 (1–2)	1.5 (1–2)	1 (1–2)	NS
BMI(kg/m2)	21.9 (19–23)	21 (19–22)	22.5 (21–24)	21.6 (19–24)	NS
FSH(mIU/ml)	5.3 (3.9–6.4)	5.7 (4.9–6.9)	5.8 (5.1–7)	5.9 (5.1–7.3)	NS
LH(mIU/ml)	6 (4.3–8.5)a	5.3 (3.9–7.3)ab	3.9 (3.1–5.6)b	5 (4–6.6)ab	< 0.05
Estradiol(pg/ml)	46.8 (36.9–57.2)	48.2 (40.2–62.2)	39.9 (34–50.4)	46.1 (34.9–56.7)	NS
T. Testosterone (ng/dl)	83(64–102)a	89 (76–108)a	55 (50–60)bc	53 (45–60)c	< 0.01
DHEAS (ng/ml)	2511 (1986–3326)ab	3130 (2491–3635)a	2093 (1735–2985)bc	2173 (1657–2549)c	< 0.01
Androstenedione(ng/ml)	2.4 (1.9–3.1)a	2.3 (1.6–2.8)ab	1.7 (1.4-2.1)bc	1.5 (1.2-1.8)c	< 0.01
HOMA-IR	2.3 (1.3–3.7)	1.6 (1.2–2.5)	1.6 (1.1–3.0)	1.5 (1–2.5)	NS
Totalcholesterol (ng/dL	165 (145–188)	156 (136–167)	162 (147–189)	155 (147–176)	NS
LDL-C(ng/dl)	107 (93–122)	101 (88–110)	104 (98–128)	101 (98–113)	NS
HDL-C(ng/dl)	49 (43–57)	51 (43–57)	48 (45–51)	50 (47–57)	NS
Triglyceride (ng/dl)	91 (80–105)	90 (79–99)	96 (86–109)	89 (76–99)	NS

Cibula et al. [23] evaluated the relationship between acne severity and the clinical and laboratory markers of androgenity in 90 women over 17 years of age. They found hirsutism in 21% of the subjects and 81% of the patients had at least one elevated serum androgen level. This result indicates a possible role of androgens in acne, however, they found that the severity of acne is not determined by serum androgen level, suggesting other factors than androgen levels in the pathogenesis of acne.

Recently, Trakasis et al. [24] investigated the prevalence of NCAH due to 21-hydroxylase deficiency in 123 women with acne. They found that 6 (4.9%) of women had NCAH according to adrenocorticotropic hormone stimulation test. However, the authors did not confirm the diagnosis by genotyping. Also, they have included patients suffering from other hyperandrogenic symptoms such as hirsutism. We did not diagnose any patient with NCAH. However, we have recruited only patients suffering from acne which might affect the diagnostic distribution of our patients.

The Amsterdam ESHRE/ASRM-sponsored third PCOS Consensus Workshop Group suggested that acne is not commonly associated with hyperandrogenemia and therefore should not be regarded as evidence of hyperandrogenemia [25]. However, the results of our study and the studies cited above suggest that acne is an important sign of androgen excess disorders and three quarters of patients with acne may have any disorder such as PCOS, IHA, IH or NCAH. By excluding acne from being a hyperandrogenic symptom, those patients may be misclassified which might affect the therapeutic approach. From the therapeutic point of view, since patients with acne may have any form of androgen excess disorder, they may require specific (antiandrogen) treatments other than local therapies for acne. Actually, treatment failures with traditional acne therapies are common in women. As many as 81% of women report failures with systemic antibiotics, and failures with isotretinoin range from 15% to 30% [26].

As in patients with IH, patients with isolated acne have lower serum androgen levels than patients with PCOS and IHA. From another point of view, 64% of patients with acne have hyperandrogenemia while 36% of the patients have normal serum androgen levels. The increased sebum production in acne patients may be due to increased circulating androgens or a hyperresponsiveness of the target organ (the pilosebaceous unit) to androgens, or both [27]. It has been hypothesized that there may be increased local production of androgens within the sebaceous glands of patients with acne [27]. Thiboutot et al. [28] investigated the role of serum androgen levels and locally produced androgens in patients with acne. They have found that although serum androgen levels were significantly higher in women with acne than those without acne, the values were still within normal range.

Similarly, previously we have shown that although serum androgen levels were within normal limits, patients with IH had (relatively) higher serum androgen levels than healthy subjects [29]. Those results suggest that although hyperandrogenemia has a role in the pathogenesis of acne, it may be seen even in patients with normal serum androgen levels and those patients may be hyperandrogenic at tissue level. In accordance, it has been suggested that hormonal therapy can be very effective in women with acne, whether or not their serum androgens are abnormal [30].

Although patients with HAA have higher insulin resistance than patients with isolated acne, the prevalence of glucose intolerance was not significantly different between groups. Moreover, both groups have similar serum lipid levels. It is well known that since glucose intolerance is a disorder of sustained insulin resistance for some years and metabolic derangements require some time for their clinical apperance, those young women may be considered as under the risk of developing glucose intolerance in their future life.

In conclusion, hyperandrogenemia is common in patients presenting with acne alone. Our data suggest that not all but in the majority of the patients, acne is not solely a cosmetic problem and the presence of androgen excess disorders should be evaluated in patients presenting with acne.

Conflict of interest

The authors declare that they have no conflict of interest.

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Authors' contribution

G. UYSAL: Data Collection, Manuscript writing
Y. SAHIN: Project development, Manuscript writing
K. UNLUHIZARCI: Manuscript writing, Project development
A. FERAHBAS: Conception and design, Project development
S.Z. ULUDAG: Analysis and interpretation of data, Data Collection
E. AYGEN: Manuscript writing, Conception and design
F. KELESTIMUR: Analysis and interpretation of data, Project development

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